Remarks

Claims 1, 3, 11 and 27-37 are pending in the subject application. New dependent Claims 38 and 39 have been added by this Amendment. Support for new Claim 38 can be found in the specification as originally filed at, *inter alia*, page 32, lines 5-7. Support for new Claim 39 can be found in the specification as originally filed at, *inter alia*, page 32, 12-13. Accordingly, applicants maintain that the amendments to the claims raise no issue of new matter and request that the amendments be entered.

35 U.S.C. §102(b) Rejection

Claims 1, 3, 11, 27 and 29-32 were rejected in the October 11, 2011 Final Office Action under 35 U.S.C. §102(b) as anticipated by WO 01/64749 ("Kloetzer"). The rejection was maintained "for reasons of record" in the January 18, 2012 Advisory Action. This rejection is respectfully traversed.

Kloetzer does not teach a method of Claim 1 or of Claim 29. As indicated in the specification at page 4, line 35 to page 5, line 1, type-1 diabetes is understood to be due to an attack by autoreactive T cells on pancreatic β-cells. The infiltration of pancreatic islets is associated with the key feature of hyperglycemia (page 5, lines 10-11), and halting or delaying β-cell destruction is a treatment strategy to halt or delay development of diabetes (page 5, lines 18-21). As indicated in applicants' specification, inhibition of progression of diabetes was observed in animals treated with anti-MIF antibodies and exposed to STZ; hyperglycemia was inhibited in those animals. In addition, islet infiltration was reduced (see page 32 of specification as filed). Furthermore, prophylactic anti-MIF treatment resulted in mice exposed to STZ remaining euglycemic (see page 32 of specification as filed), thus inhibiting development of diabetes. Also, islet inflammation was attenuated. These are, as described in the specification, anti-diabetogenic effects.

The condition known as diabetic neuropathy, in contrast, is an eye disease which is characterized by lesions in the retina and is a disorder in its own right that can occur in subjects who do not have diabetes (as shown by the American Diabetic Association reference submitted previously). In addition, while the January 18, 2012 Advisory Action maintains that treatment of diabetic retinopathy is encompassed by the claims, the claim language (e.g. Claim 1) clearly states "inhibiting the progression of type 1 diabetes" (Claim 1) or inhibiting development of type 1 diabetes" (Claim 29), not treating a retinopathy.

As stated in MPEP §2131.02: " '[t]he identical invention must be shown in as complete detail as is contained in the ... claim.' Richardson v. Suzuki Motor Co., 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989)." (Emphasis added). Because Kloetzer does not disclose the identical invention, the anticipation rejection is not proper and should be withdrawn.

35 U.S.C. § 103(a) Rejection

Bojunga in view of Nishihira & Ogata

Claims 1, 3, 11, 27, and 29-32 were rejected under 35 U.S.C. §103(a) as unpatentable over Bojunga et al. ("Bojunga") in view of Nishihira and Ogata ("Nishihira"). This rejection is respectfully traversed.

The rejection is premised on the assertion that Bojunga teaches treatment of diabetes with an MIF inhibitor. Nishihira is additionally asserted as support for the notion that anti-MIF antibodies and small organic molecules are interchangeable.

Bojunga (i) experimentally induces diabetes and looks at the accompanying MIF *nucleic acid* levels and (ii) determines that MIF-mRNA expression was elevated in the splenic lymphocytes of NOD mice in which diabetes spontaneously occurred. However, as pointed out in applicants' specification, e.g. at page 31, line 21 to 23, while it was

known that "MIF *mRNA* expression is up-regulated in spontaneously diabetic NOD mice," MIF protein's "functional role in disease progression" was unknown. Bojunga, which (i) did not measure any increases in native MIF protein level changes in association with diabetes, and in fact (ii) measured decreased lymphocyte MIF protein levels in diabetic mice, and which (ii) did not find any statistically significant correlation between MIF and diabetes, did not change this situation.

Moreover, as pointed out by applicant with the previous submission of the article Greenbaum et al., the art makes it clear it is not reasonably predictable whether raised mRNA levels are correlated with raised levels of the encoded protein. To quote Greenbaum et al., "[a]ttempts to correlate protein abundance with mRNA expression levels have had variable success." Applicant has also previously provided, in the form of Ogata et al., a specific example for the relevant protein, MIF, where high MIF mRNA expression was not positively correlated with high MIF protein levels[1]. In addition, it is noted that while the Final Office Action emphasizes that, in Ogata, expression did not correlate in only "a single cell type", applicant notes that only two cell types were tested in Ogata, and no correlation was found in one type. In Bojunga, the primary reference, one cell type was tested and no correlation was found. Thus, Ogata and Bojunga do not show a predictable correlation.

In light of Ogata, Bojunga and Greenbaum, which are examples of the art at the time of filing, MIF protein levels were not reasonably predictable from MIF mRNA levels. This is significant because the rejection over the primary reference Bojunga is based on the concept that increased native MIF protein levels increases diabetes incidence. Bojunga shows no such relationship and asserts the correlation between diabetes incidence in the test mice (i.e. NOD mice which are susceptible to spontaneous

[1] Whilst the Final Office Action asserts that "this can easily be explained by either secretion or degradation of the protein" other possible explanations include the failure, inhibition or regulation of one or more steps between transcription and translation. In any event, all of these possibilities underline the unpredictability of the relationship between mRNA levels and encoded protein levels and that it is not predictable that raised MIF mRNA levels *in vivo* correlates with raised MIF protein levels.

development of autoimmune diabetes) and *exogenously* added MIF was not statistically significant. As summarized by Bojunga in the Abstract "our preliminary study suggests a possible role of MIF in autoimmune inflammatory events." Bojunga's speculation on "possible" role for MIF in autoimmune inflammatory events is couched in language which points to the unpredictability of any related therapeutic strategy. In addition, the hypothetical therapeutic strategy is not specified, it is not clear if it is directed to autoimmune inflammatory events in general, or to diabetes, and whether it involves, for example, a manipulation of MIF mRNA levels.

The secondary reference Nishihira is cited in the Office Action in combination with Bojunga for the notion that "small organic molecules are interchangeable with antibodies in the context of treatment of autoimmune disease", with the "Perspectives" section of Nishihira is identified as the source of this assertion. However, the only sentence in the Perspectives section regarding antibodies states "the therapeutic use of anti-MIF antibodies and small molecules inhibiting MIF activity could be promising for septic shock..." (Emphasis added). There is no statement or implication for the notion of interchangeability here. If there is support for such a notion in Nishihira, applicant requests that the Examiner point out the support by page number and position so that they may better respond to this assertion. Otherwise, applicant requests that this assertion of "interchangeability" be withdrawn as it is appears to have no actual basis in the cited art.

The teachings of Bojunga and Nishihira combined do not suggest the invention as claimed, and support the unpredictability, prior to applicant's disclosure of increased MIF protein levels in diabetic pancreas and peritoneal cells, of inhibiting the progression of type 1 diabetes in a mammal having type 1 diabetes using an agent comprising a binding site of an MIF antibody. Moreover, the differences between the cited art and the claimed invention are not obvious (MPEP §2141 (III)). Accordingly, applicant respectfully request that the Examiner reconsider and withdraw this rejection.

Bojunga in view of Nishihira and U.S. Patent No. 5,530,101

Claims 28 and 33 were rejected under 35 U.S.C. §103(a) as unpatentable over Bojunga in view of Nishihira as applied to Claims 1, 3, 11 and 27 above, and further in view of U.S. Patent No. 5,530,101 ("Queen"). The asserted teachings of Bojunga and Nishihira are described above, and Queen is cited for the notion of humanized monoclonal antibodies. This rejection is respectfully traversed.

As discussed above, the claimed invention is patentable over Bojunga in view of Nishihira because of the unpredictability and for the lack of teaching or suggesting of all the elements of the claim (the differences not being obvious; MPEP §2141 (III)). The addition of Queen does not remedy the failure of Bojunga and Nishihira to render the claimed method obvious. More specifically, Queen was cited for describing the production of humanized antibodies but Queen suggests nothing that would render the claimed method, regarding the use of MIF antibodies for inhibiting progress or development of type 1 diabetes, obvious. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

WO 01/32606 and Nishihira

Claims 1, 3, 11, 27 and 29-32 were rejected under 35 U.S.C. §103(a) as unpatentable over WO 01/32606 in view of Nishihira as cited above. This rejection is respectfully traversed.

WO 01/32606 describes small molecules having MIF antagonist activity and compounds for the treatment of inflammatory disorders. However, WO 01/32606 does not provide any data showing any of its compounds are indeed useful for inhibiting the progress of type 1 diabetes in a subject having type 1 diabetes, or can be used to inhibit the development of type 1 diabetes in a subject at risk for type 1 diabetes. Furthermore, with respect to MIF antibodies, WO 01/32606 teaches that "such biological agents, unfortunately, have certain limitations with regard to their clinical utility. Therefore there is a need in the art to discover and develop small organic molecules that function

as MIF antagonists..." (WO 01/32606, page 2). Thus, while WO 01/32606 is being cited for the notion of treating an inflammatory disease with an anti-MIF agent, it indicates antibodies are problematic and that "[t]herefore there is a need in the art to discover and develop small organic molecules." Moreover, the remaining pages of the publication do not refer to antibodies and instead regard non-antibody small molecules (Schiff base condensation products) to fulfill that stated need. Clearly, one skilled in the art, reading WO 01/32606, and without using impermissible hindsight, would consider WO 01/32606 as teaching a small molecule solution to the problem of anti-MIF biological agents being inadequate.

The non-obviousness of the claimed method in view of the teaching away from using an MIF antibody for therapeutic use is not remedied by combination with Nishihira which describes the use of MIF as a target molecule in multiple sclerosis, not type 1 diabetes.

For these reasons, the claimed invention is not obvious over WO 01/32606 and Nishihira. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

WO 01/32606 in view of Nishihira and Queen

Claims 28 and 33 were rejected under 35 U.S.C. §103(a) as being unpatentable over WO 01/32606 in view of Nishihira. This rejection is respectfully traversed.

As discussed above, the claimed invention is patentable over WO 01/32606 and Nishihira. The addition of Queen does not remedy the failure of Bojunga and Nishihira to render the claimed method obvious. More specifically, Queen was cited for describing the production of humanized antibodies but Queen suggests nothing that would render the claimed method, regarding the use of MIF antibodies for inhibiting progress or development of type 1 diabetes, obvious. Accordingly, reconsideration and withdrawal of this rejection is respectfully requested.

Information Disclosure Statement

The Examiner indicated that certain previously submitted information on form PTO/SB/08b was not considered for formalities with the recitations. In this regard, applicant submitted with the previous response a copy of a new PTO/SB/08b addressing the issues enumerated on the PTO/SB/08b previously returned to applicant.

The January 18, 2012 Advisory Action indicates that the PTO/SB/08b was not considered because the "fee and assurances/statements have not been submitted." In this regard, applicant notes that new information was not being submitted, and in fact all the items for consideration were previously submitted and are available in the IFW. Applicant was submitting a PTO/SB/08b complying with the Examiner's requirements. Accordingly, applicant respectfully requests return of the PTO/SB/08b indicating the items have been considered. For the purposes of convenience, applicant is filing herewith by EFS a further copy of the relevant PTO/SB/08b. In addition, applicant is submitting a second PTO/SB/08b disclosing a new item of information. As this is being submitted under 37 C.F.R. §1.97(b)(4), no fee is deemed necessary.

Conclusion

In view of the preceding amendment and remarks, applicant respectfully requests that the Examiner reconsider and withdraw the rejections in the October 11, 2011 Final Office Action, and earnestly solicit allowance of the pending claims. If there is any minor matter preventing the allowance of the subject application, the Examiner is requested to telephone the undersigned attorney.

No fee, other than the total fee of $745, which includes a $465 RCE fee and a $280 one-month extension fee, and which total fee is hereby authorized to be charged to Deposit Account No. 01-1785, is deemed necessary in connection with the filing of this Communication and RCE. If any additional fee is required to preserve the pendency of the subject application or for consideration of the IDS, authorization is hereby given to charge such fee to Deposit Account No. 01-1785.

Respectfully submitted,

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